Context-Dependent Enhancement of Induced Pluripotent Stem Cell Reprogramming by Silencing Puma.

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Authors: B B Lake, J Fink, L Klemetsaune, X Fu, J R Jeffers, G P Zambetti, Y Xu

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Public Summary:
Induced pluripotency has been associated with genomic instability that can significantly impair the therapeutical potential of iPSCs in human therapy. We are investigating the underlying basis by studying the tumor suppression pathways that are selectively impaired during the reprogramming. Our studies have identified multiple pathways involved in suppressing the induced pluripotency and shed light on the possibility to increase the reprogramming efficiency without negative impact on genomic stability.

Scientific Abstract:
Reprogramming of the somatic state to pluripotency can be induced by a defined set of transcription factors including Oct3/4, Sox2, Klf4 and c-Myc [1]. These induced pluripotent stem cells (iPSCs) hold great promise in human therapy and disease modeling. However, tumor suppressive activities of p53, which are necessary to prevent persistence of DNA damage in mammalian cells, have proven a serious impediment to formation of iPSCs [2]. We examined the requirement for downstream p53 activities in suppressing efficiency of reprogramming as well as preventing persistence of DNA damage into the early iPSCs. We discovered that the majority of the p53 activation occurred through early reprogramming-induced DNA damage with the activated expression of the apoptotic inducer Puma and the cell cycle inhibitor p21. While Puma-deficiency increases reprogramming efficiency only in the absence of c-Myc, double deficiency of Puma and p21 has achieved a level of efficiency that exceeded that of p53 deficiency alone. We further demonstrated that, in both the presence and absence of p21, Puma-deficiency was able to prevent any increase in persistent DNA damage in early iPSCs. This may be due to a compensatory cellular senescent-response to reprogramming-induced DNA damage in pre-iPSCs. Therefore, our findings provide a potentially safe approach to enhance iPSC derivation by transiently silencing Puma and p21 without compromising genomic integrity.